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(54) Title: BIOCOMPATIBLE COATING, MEDICAL DEVICE USING THE SAME AND METHODS

(57) Abstract

The invention involves using a plasma to functionalize a surface of medical devices such as catheters, particularly intracardial catheters, with covalently bound thermochemically reactive groups. The surface is further contacted with a bioactive agent, particularly antithrombogenic coatings, which is thermochemically covalently coupled to the reactive group to form a therapeutically effective coating. The selected bioactive agent is then covalently bound to the surface by thermochemical reaction with the surface reactive groups. In another embodiment, the functionalizing step comprises contacting the surface with a Langmuir-Blodgett film comprising an amphipathic compound and a bioactive agent and using a plasma to covalently crosslink the Langmuir-Blodgett film to the medical device surface and to the bioactive agent. Medical devices prepared by the subject methods are also provided.

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BIOCOMPATIBLE COATING, MEDICAL DEVICE USING THE SAME AND METHODS

The Field of the invention is biocompatible coatings of medical devices, particularly antithrombogenic coatings for intravascular catheters.

Medical devices which have direct contact with blood flow have a tendency to promote localized thrombosis. Additionally, it is often desirable to promote localized thrombosis at the sites of wounds. The present invention provides novel methods for applying therapeutic coatings such as thrombogenic and antithrombogenic coatings to a variety of medical devices.

SUMMARY OF THE INVENTION

The invention provides covalently attached therapeutic coatings for surfaces of medical devices and a variety of methods for making medical devices with such coatings.

In one embodiment, the methods involve functionalizing a surface of the medical device with covalently bound thermochemically reactive groups. The surface is further contacted with a bioactive agent which is thermochemically covalently coupled to the reactive group to form a therapeutically effective coating. In a preferred embodiment, the functionalizing step comprises contacting the surface with a plasma to form the thermochemically reactive groups. A wide variety of reactive groups which

provide convenient reactants for the selected bioactive agent may be used. The selected bioactive agent is then covalently bound to the surface by thermochemical reaction with the surface reactive groups.

In another embodiment, the functionalizing step comprises contacting the surface with a Langmuir-Blodgett film comprising an amphipathic compound and a bioactive agent. A plasma or thermochemical means are then used to covalently crosslink the Langmuir-Blodgett film to the medical device surface and to the bioactive agent. Optionally, in this embodiment, the surface may also be functionalizing with a first thermochemically reactive group capable of reacting with at least one of the amphipathic compound and the bioactive agent. Similarly, the bioactive agent may be derivatized with a second reactive group capable of reacting with the first reactive group.

In these methods, the bioactive agent is advantageously derivatized with a label capable of providing a detectable signal. Hence the detectable signal is used to quantify the bound bioactive agent on the device's surface.

Where the bioactive agent is antithrombogenic, it may be a relatively irreversible thrombin inhibitor, such as D-Phe-Pro-Arg-chloromethyl ketone, or a relatively reversible thrombin inhibitor, such as heparin or a polypeptide comprising the amino acid sequence Ile-Pro-Glu-Glu-Tyr-Leu-Gln.

Exemplary medical devices for antithrombogenic coatings include catheters, particularly intracardial catheters, vasculature stents and grafts and various blood transfer devices such as blood oxygenators, dialysis and plasmapheresis devices, etc. Exemplary medical devises for thrombogenic coatings include wound closing and wound covering devises such as sutures, bandages, etc.

The medical devices of the invention have a surface with a covalently attached dry therapeutic coatings. In one embodiment, the coating comprises thermochemically reactive groups covalently bound to the surface and a bioactive agent covalently bound to a portion but fewer than all of the thermochemically reactive groups. In another embodiment, the coating comprises a Langmuir-Blodgett film comprising an amphipathic compound and a bioactive agent, where the amphipathic compound is covalently crosslinked to the surface, and the bioactive agent is covalently crosslinked to the amphipathic compound.

The invention also provides general methods for treating a surface of a medical device with a therapeutic covalent coating of a bioactive agent; thereafter, washing the surface to remove any bioactive agent which is not covalently bound; thereafter, causing a reagent capable of selectively, non-covalently binding to the bioactive agent to become selectively and non-covalently bound to the bioactive agent; thereafter, washing the surface to remove any of such reagent which is not selectively bound to the bioactive agent; thereafter, detecting a radiative signal at an intensity which meets or exceeds a predetermined intensity which correlates with the presence of coating of a predetermined amount of the bioactive agent covalently bound to the surface. For example, the reagent may be a specific antibody and the signal fluorescence.

DESCRIPTION OF THE DRAWINGS

FIG. 1 shows a typical plasma chamber.

FIG. 2 shows a typical plasma surface modification system.

FIG. 3 shows a catheterized heart.

FIG. 4 shows a typical electrophysiology catheter.

FIG. 5 shows a typical stent.

FIG. 6 shows a typical blood oxygenator.

DETAILED DESCRIPTION OF THE INVENTION

The invention provides a wide variety of covalently attached biocompatible coatings for surfaces of medical devices. In particular embodiments, the invention provides covalently attached antithrombogenic coatings for medical devise surfaces exposed to blood flow and thrombogenic coatings for medical devise surfaces not exposed to blood flow continuous with bodily circulation. The invention provides a variety of methods for making medical devices with such coatings.

The methods involve functionalizing the selected surface of a medical device with covalently bound reactive groups. The surface is further contacted with a bioactive agent, in particular an antithrombogenic agent, which is covalently coupled to the reactive group to form a coating effective to inhibit the formation of thrombus when the surface is exposed to blood flow continuous with bodily blood circulation. While described below primarily with antithrombogenic agents, it is understood that a wide variety of bioactive agents, e.g., antibiotics, may be substituted for the antithrombogenic agents, depending on the desired characteristics of the device's surface.

In one embodiment, the functionalizing step comprises contacting the surface with a plasma to form chemically reactive groups. The plasma used in this method are conveniently "low temperature" or "cold" plasma produced by glow discharge. A low temperature plasma is created in evacuated chamber refilled with a low pressure gas. The pressures are typically in the order of 0.1 to 10 torr and the gas is excited by electrical energy in the radio frequency range (RF). The glow discharge, typically in the range of 100 to 1,000 watts, depending on the chamber

volume, contains ions, electrons, metastables, and photons. When these species interact with the surface a variety of reactions can take place. Bonds can be broken, new bonds are formed, and if a reactive gas is used this can also react with the substrate.

A wide variety of reactive groups which provide convenient reactants for the selected bioactive agent may be used. For example, hydroxyl groups are attached to the surface either with use of methane/oxygen plasma or water/oxygen plasma. A carboxyl rich surface are generated by the deposition of acrylic acid to the surface of the device. Frequently, the reactant is provided with a carrier gas; for example, methane gas which additionally provides surface polyalkyl (hydrocarbon) chains may be advantageously used where otherwise unreactive metal surfaces are to be coated. Alternatively, an inert carrier gas such as helium or argon may be used. Typically the gas/reactant are introduced in a ratio of approximately 3:1.

Device surfaces are typically treated for from about 0.5 to about 30 minutes, desirably obtaining a uniform distribution of amine on the plastic surface. The water surface tension of the modification may be confirmed by the water contact angle measurements.

The selected bioactive agent is covalently bound to the surface by thermochemical reaction with the surface reactive groups. For example, carboxyl groups readily react with xylose moieties on heparin in the presence of 1-ethyl-3(-dimethylaminopropyl) carbodiminde, EDC, to form an ester linkage. Hirudin and its analogs are conveniently bound to carboxyl rich surface by introduction of specifically engineered amino group at the carboxyl terminus of the peptide away from the active amino terminus.

In another embodiment, the functionalizing step comprises contacting the surface with a Langmuir-Blodgett film

comprising an amphipathic compound and a bioactive agent. A crosslinking agent is then used to covalently crosslink the Langmuir-Blodgett film to the medical device surface and to the bioactive agent. For example, an argon or helium plasma chamber is used to contact the Langmuir-Blodgett film-coated surface with high energy photons and electrons capable of chemically crosslinking the amphipathic compound and the bioactive agent. The amphipathic compound and bioactive agent may be applied sequentially or simultaneously. Similarly, the surface-amphipathic compound crosslinking and amphipathic compound-bioactive agent crosslinking may be performed either sequentially or simultaneously. Optionally, in this embodiment, the surface may also be functionalizing with a first reactive group capable of reacting with at least one of the amphipathic compound and the bioactive agent. Similarly, the bioactive agent may be derivatized with a second reactive group capable of reacting with the first reactive group.

In these methods, the bioactive agent is advantageously derivatized with a label, particularly a fluorescent or colorimetric label, capable of providing a detectable signal. Hence the detectable signal is used to quantify the bound bioactive agent on the device's surface.

Where an antithrombogenic agent is used, it may be a relatively irreversible thrombin inhibitor, such as D-Phe-Pro-Arg-chloromethyl ketone, or a relatively reversible thrombin inhibitor, such as heparin or a polypeptide comprising the amino acid sequence Ile-Pro-Glu-Glu-Tyr-Leu-Gln. Prothrombogenic agents include thromboplastin, thrombocytin, and other clotting factors. Other useful bioactive agents include antimicrobial and antifungal agents, growth factors, etc.

For antithrombogenic coatings, the medical device has a surface destined for contact with blood flow continuous with bodily blood circulation as distinguished from blood

permanently removed from bodily circulation. Exemplary devices include catheters, particularly intracardial catheters, vasculature stents and grafts and various blood transfer devices such as blood oxygenators, dialysis and plasmapheresis devices, etc. In a specific embodiment, the medical device is an intracardial a catheter probe for introduction into a chamber of the heart, having proximal and distal extremities and comprising a flexible elongate tubular member having at least one lumen extending therethrough extending the length thereof and having a distal extremity, a plurality of longitudinally and radially spaced apart electrodes, expandable means secured to the distal portion of said flexible elongate tubular member and being movable between a contracted position and an expanded position, means mounting said electrodes on said expandable means whereby when said expandable means is moved to the expanded position in the chamber of the heart the electrodes are moved into engagement with the wall forming the chamber of the heart, means coupled to the expandable means for moving said expandable between said contracted and expanded positions, said expandable means including a plurality of plastic elements having surfaces exposed to the blood and said elements having spaces therebetween when in the expanded position through which the blood can flow, lead means for conducting electrical energy in contact with the electrodes and extending into said flexible elongate tubular member and electrical means connected to said lead means for performing electrical functions with respect to said electrodes.

Medical devices suitable for thrombogenic coatings include devices for occluding aneurysms or ruptured vessels, for closure of percutaneous or vascular puncture sites, etc. For example, the proximal end of the introducer of such devices as laproscopes, catheters, etc., may also be advantageously so coated.

Many of the subject medical devices of the invention have a blood flow-contacting surface with a covalently attached dry coating to inhibit thrombosis. In one embodiment, the coating comprises reactive linking groups covalently bound to the surface and a bioactive agent covalently bound to a portion but fewer than all of the reactive linking groups. In another embodiment, the coating comprises a Langmuir-Blodgett film comprising an amphipathic compound and a bioactive agent, where the amphipathic compound is covalently crosslinked to the surface, and the bioactive agent is covalently crosslinked to the amphipathic compound.

The invention also provides general methods for treating a surface of a medical device to inhibit thrombosis which involve causing a bioactive agent to become covalently bound to a medical device surface exposed to blood flow continuous with bodily blood circulation; thereafter, washing the surface to remove any bioactive agent which is not covalently bound; thereafter, causing a reagent capable of selectively, non-covalently binding to the bioactive agent to become selectively and non-covalently bound to the bioactive agent; thereafter, washing the surface to remove any of such reagent which is not selectively bound to the bioactive agent; thereafter, detecting a radiative signal at an intensity which meets or exceeds a predetermined intensity which correlates with the presence of coating of a predetermined amount of the bioactive agent covalently bound to the surface. For example, the reagent may be a specific antibody and the signal fluorescence.

EXAMPLES

In a specific case, an antithrombogenic coating was applied to surface of an electrophysiology catheter by this method. The catheter made of PBax tubing loaded with barium salt. The distal end of catheter had annular platinum electrodes and a platinum cap. First the catheter was placed in the plasma chamber and evacuated. A mixture of methane (490

SCCM) and ammonia (161 SCCM) were introduced into the chamber maintained at 0.265 tort pressure. A 400 watts glow discharge established between the electrodes. The sample was treated for 3 minutes under the conditions. Under these condition there uniform distribution of amine on the plastic surface. Between 40 to 100 of the surface is covered by amine groups. The modification was confirmed by the water contact angle measurements. The contact angle was 85 degrees for the untreated sample the treated sample had contact angle of 41 degrees.

The bioactive agent was derivatized when necessary to improve the covalent binding to the device. In case of heparin, the xylose can be reacted with the carboxyl group on the plasma treated surface by simple esterification in the presence of 1-ethyl-3-(3-dimethylaminopropyl) carbodimide (EDC). 200 mg of EDC was dissolved in the 5 ml of water and pH was adjusted to 4 with dilute hydrochloric acid. The device was immersed in this solution. Heparin (200,000 units) dissolved in 5 ml of water was added to this. The pH was adjusted to 4 again. The solution was periodically stirred for two hours at room temperature. Additional 100 mg of EDC was added and the reaction continued for 12 hrs. The device was then washed with phosphate buffered saline to remove unreacted heparin. The device was then air dried and stored moisture free.

The effectiveness of the coating was determined by in-vitro by blood clotting time. Citrated cow blood was incubated at 37oC. Heparin coated device was immersed in the blood. The clotting was initiated by the addition of 2-3 drops of 10% calcium chloride solution. Control tubes with no device and uncoated device were also maintained. The time for clot formation was determined by examining the test tube periodically. In the control tests tube the clotting started in less then 15 minutes. Heparin coated devices prevented the clotting at least for 2 hrs.

In vivo, studies were conducted in sheep. The coated device was introduced to left ventricle. After leaving the device in place for one hour the device was withdrawn. The device was gentle rinsed in saline and the surface was examined for thrombus. With a good Heparin coating very little or no thrombus formation was observed.

The stability of coating was determined by extracting the device in saline for 1 to 24 hrs. at 37°C and then performing the in vitro studies described above. There was no substantial difference in the clotting times for the saline extracted devices. Nearly all the heparin is covalently bound to the device.

In another example, in a Langmuir-Blodgett trough, a laminar flow of water at 1 gallon/hr. was established. At one end of the trough a dispenser a solution of an amphophilic molecules in a water miscible solvent such as acetone is dispensed at controlled rate. The amphophilic molecules will spread on the surface of the water and form a film. If they are rod like molecules, they tend to align within this film. By controlling the dispensing rate of the amphophil, the thickness or the number mono layer in the film can be controlled. When a device such as a catheter is immersed in the water and slowly withdrawn, the film is transferred to the device surface. The film thus transferred can be dried on surface to give a highly oriented coating. Additional layers of the coating can be applied by repeated dipping and drying. A multi-layer coating can be annealed to get interpenetration of the layers. LB film are not generally very stable. If a device coated with LB film is subjected, plasma treatment covalent bond can be generated between the rods and between the device and the film. Such a crosslinked coating is very robust. To a LB trough with laminar water flow, a solution of gamma-methyl-L-glutamate-gamma-n-octadecyl-L-glutamate copolymer dispensed through a narrow slot just touching the water surface. The rate was

controlled to attain a double layer of glutamate polymer. The film was transferred to a intercardial catheter made of polyethylene and gold sensing elements. The film was air dried at 45°C for 1 hr. This was then coated for a second time with a layer of hirudin derivatized at the corboxyl terminus with octadecyl-L-glutamate. The second bioactive layer was air dried as before. Then this device was placed in a plasma chamber and subjected to an argon glow discharge for 3 mins. at 300 watts. The high energy particle induce high reactive free radicals with in the LB film. These radical then covalently link the aligned film components as well as the film to the substrate. Poly (tetramethoxytertraoctoxyphthalocyainato) polysiloxane, isopentyl cellulose and butylcellulose are other examples of materials that are hairy rods that form nice LB films. A variety of bioactive peptides can be derivatized to form self assembled films.

The device can be functionalized first with plasma to have reactive function such as carboxyl, hydroxyl, carbonyl or amine group before LB film deposition. This then can be subjected as a procedure as described above.

The LB film layer can also be formed by a mixture of the rod-like amphipiles and the derivatized biomolecule in a single dip process. This will give a coating of amphiphiles interspersed with bioactive moieties. This then can be covalently linked using inert gas plasma.

WHAT IS CLAIMED IS:

1. A method for treating a surface of a medical device to inhibit thrombosis comprising steps:

functionalizing a surface of a medical device which surface is exposed to blood flow continuous with bodily blood circulation with a first reactive group, contacting said surface with an antithrombogenic agent capable of reacting with said first reactive group, and causing said antithrombogenic agent to react with said first reactive group to covalently bind said antithrombogenic agent to said surface to form a coating on said surface which coating is effective to inhibit the formation of thrombus when said surface is exposed to blood flow continuous with bodily blood circulation.

2. A method according to claim 1 wherein said functionalizing step comprises contacting said surface with a plasma.

3. A method according to claim 1 wherein said contacting step comprises contacting said surface with an antithrombogenic agent derivatized with a second reactive group capable of reacting with said first reactive group to covalently bind said antithrombogenic agent to said surface.

4. A method according to claim 1, wherein said contacting step comprises contacting said surface with an antithrombogenic derivatized with a label, wherein said label is capable of providing a detectable signal.

5. A method according to claim 1, wherein said contacting step comprises contacting said surface with an irreversible thrombin inhibitor.

6. A method according to claim 1, wherein said contacting step comprises contacting said surface with an reversible thrombin inhibitor.

7. A method according to claim 1, wherein said contacting step comprises contacting said surface with D-Phe-Pro-Arg-chloromethyl ketone.

8. A method according to claim 1 wherein said contacting step comprises contacting said surface with heparin.

9. A method according to claim 1 where said contacting step comprises contacting said surface with a polypeptide comprising the amino acid sequence Ile-Pro-Glu-Glu-Tyr-Leu-Gln.

10. A method according to claim 1 wherein said functionalizing step comprises functionalizing a surface of a catheter, stent, graft, or blood transfer device.

11. A method according to claim 1 for treating a surface of an intracardial catheter probe which is exposed to blood within a body to inhibit formation of thrombus, wherein said catheter probe is for introduction into a chamber of the heart, has proximal and distal extremities and comprises a flexible elongate tubular member having at least one lumen extending therethrough extending the length thereof and having a distal extremity, a plurality of longitudinally and radially spaced apart electrodes, expandable means secured to the distal portion of said flexible elongate tubular member and being movable between a contracted position and an expanded position, means mounting said electrodes on said expandable means whereby when said expandable means is moved to the expanded position in the chamber of the heart the electrodes are moved into engagement with the wall forming the chamber of the heart, means coupled to the expandable means for moving said expandable means between said contracted and expanded positions, said expandable means including a plurality of plastic elements having surfaces exposed to the blood and said elements having spaces therebetween when in the expanded position through which the blood can flow, lead means for conducting electrical energy

in contact with the electrodes and extending into said flexible elongate tubular member and electrical means connected to said lead means for performing electrical functions with respect to said electrodes, said method comprising steps: functionalizing a surface of said intracardial medical device with a first reactive group, contacting said surface with an antithrombogenic agent capable of reacting with said first reactive group, and causing said antithrombogenic agent to react with said first reactive group to covalently bind said antithrombogenic agent to said surface to form a coating on said surface which is effective to inhibit the formation of thrombus when said surface is exposed to blood within a body.

12. A medical device having a surface, said surfacing having a covalently attached coating to inhibit thrombosis, said coating being a dry coating comprising a plurality of reactive groups covalently bound to said surface and an antithrombogenic agent covalently bound to a portion but fewer than all of said reactive groups and said coating is effective to inhibit the formation of thrombus when said surface is exposed to blood flow continuous with bodily blood circulation.

13. A medical device according to claim 12 comprising an intracardial medical device comprising a catheter probe for introduction into a chamber of the heart, having proximal and distal extremities and comprising a flexible elongate tubular member having at least one lumen extending therethrough extending the length thereof and having a distal extremity, a plurality of longitudinally and radially spaced apart electrodes, expandable means secured to the distal portion of said flexible elongate tubular member and being movable between a contracted position and an expanded position, means mounting said electrodes on said expandable means whereby when said expandable means is moved to the expanded position in the chamber of the heart the electrodes are moved into engagement with the wall forming the chamber

of the heart, means coupled to the expandable means for moving said expandable means between said contracted and expanded positions, said expandable means including a plurality of plastic elements having surfaces exposed to the blood and said elements having spaces therebetween when in the expanded position through which the blood can flow, lead means for conducting electrical energy in contact with the electrodes and extending into said flexible elongate tubular member and electrical means connected to said lead means for performing electrical functions with respect to said electrodes, and having a surface which is exposed to blood within a body, said surface having a covalently attached coating, said coating being a dry coating comprising a plurality of reactive groups covalently bound to said surface and heparin covalently bound to a portion but fewer than all of said reactive groups and said coating being effective to inhibit the formation of thrombus when said surface is exposed to blood within a body.

14. A method for treating a surface of a medical device to inhibit thrombosis comprising steps:

contacting a surface of a medical device which surface is exposed to blood flow continuous with bodily blood circulation with a Langmuir-Blodgett film comprising an amphipathic compound;

contacting said surface with an antithrombogenic agent;

covalently crosslinking said antithrombogenic agent with said amphipathic compound covalently crosslinking said amphipathic compound to said surface;

to form a coating on said surface which coating is effective to inhibit the formation of thrombus when said surface is exposed to blood flow continuous with bodily blood circulation.

15. A method according to claim 14, wherein at least one of said crosslinking steps comprises contacting said surface with a plasma.

16. A method according to claim 14, wherein said coating steps are performed simultaneously.

17. A method according to claim 14, wherein said crosslinking steps are performed simultaneously.

18. A method according to claim 14, further comprising prior to said coating said surface with a Langmuir-Blodgett film:

functionalizing said surface with a first reactive group capable of reacting with at least one of said amphipathic compound and said antithrombogenic agent.

19. A method according to claim 18, wherein said antithrombogenic agent is derivatized with a second reactive group capable of reacting with said first reactive group.

20. A method according to claim 1, wherein contacting said surface with an antithrombogenic agent comprises contacting said surface with an antithrombogenic derivatized with a label, wherein said label is capable of providing a detectable signal.

21. A medical device having a surface, said surface having a covalently attached coating to inhibit thrombosis, said coating being a dry coating comprising a Langmuir-Blodgett film comprising an amphipathic compound and an antithrombogenic agent, said amphipathic compound being covalently crosslinked to said surface, and an antithrombogenic agent covalently crosslinked to said amphipathic compound, said coating being effective to inhibit the formation of thrombus when said surface is exposed to blood flow continuous with bodily blood circulation.

22. A method for treating a surface of a medical device to inhibit thrombosis comprising steps:

contacting an antithrombogenic agent with a surface of a medical device which surface is exposed to blood flow continuous with bodily blood circulation; thereafter

causing said antithrombogenic agent to become covalently bound to said surface; thereafter,

washing said surface to remove from said surface any of said antithrombogenic agent which is not covalently bound to said surface; thereafter,

contacting said surface with a reagent capable of selectively, non-covalently binding said antithrombogenic agent;

causing said reagent to become selectively and non-covalently bound to said antithrombogenic agent; thereafter,

washing said surface to remove from said surface any of said reagent which is not selectively bound to said antithrombogenic agent; thereafter,

detecting a radiative signal at an intensity which meets or exceeds a predetermined intensity, wherein a radiative signal at said predetermined intensity correlates with the presence of coating of a predetermined amount of said antithrombogenic agent covalently bound to said surface, said coating being effective to inhibit the formation of thrombus when said surface is exposed to blood flow continuous with bodily blood circulation.

23. A method according to claim 22, wherein said reagent is an antibody and said radiative signal is fluorescence.

24. A method for treating a surface of a medical device to provide said surface with a therapeutic coating comprising steps:

functionalizing a surface of a medical device which surface is exposed to blood flow continuous with bodily blood circulation with a first reactive group, contacting said surface with a bioactive agent capable of reacting with said first reactive group, and causing said bioactive agent to react with said first reactive group to covalently bind said bioactive agent to said surface to form a coating on

said surface which coating is therapeutic when said surface is exposed to blood flow continuous with bodily blood circulation.

25. A medical device having a surface, said surface having a covalently attached therapeutic coating, said coating being a dry coating comprising a plurality of reactive groups covalently bound to said surface and an bioactive agent covalently bound to a portion but fewer than all of said reactive groups and said coating is therapeutic when said surface is exposed to blood flow continuous with bodily blood circulation.

26. A method for treating a surface of a medical device to provide said surface with a therapeutic coating comprising steps:

contacting a surface of a medical device which surface is exposed to blood flow continuous with bodily blood circulation with a Langmuir-Blodgett film comprising an amphipathic compound;

contacting said surface with an antithrombogenic agent;

covalently crosslinking said bioactive agent with said amphipathic compound covalently crosslinking said amphipathic compound to said surface;

to form a coating on said surface which coating is effective to inhibit the formation of thrombus when said surface is exposed to blood flow continuous with bodily blood circulation.

27. A medical device having a surface, said surface having a covalently attached therapeutic coating, said coating being a dry coating comprising a Langmuir-Blodgett film comprising an amphipathic compound and an bioactive agent, said amphipathic compound being covalently crosslinked to said surface, and an bioactive agent covalently crosslinked to said amphipathic compound, said coating is therapeutic

when said surface is exposed to blood flow continuous with bodily blood circulation.

28. A method for treating a surface of a medical device to provide said surface with a therapeutic coating comprising steps:

contacting an bioactive agent with a surface of a medical device which surface is exposed to blood flow continuous with bodily blood circulation; thereafter

causing said bioactive agent to become covalently bound to said surface; thereafter,

washing said surface to remove from said surface any of said bioactive agent which is not covalently bound to said surface; thereafter,

contacting said surface with a reagent capable of selectively, non-covalently binding said bioactive agent;

causing said reagent to become selectively and non-covalently bound to said bioactive agent; thereafter,

washing said surface to remove from said surface any of said reagent which is not selectively bound to said bioactive agent; thereafter,

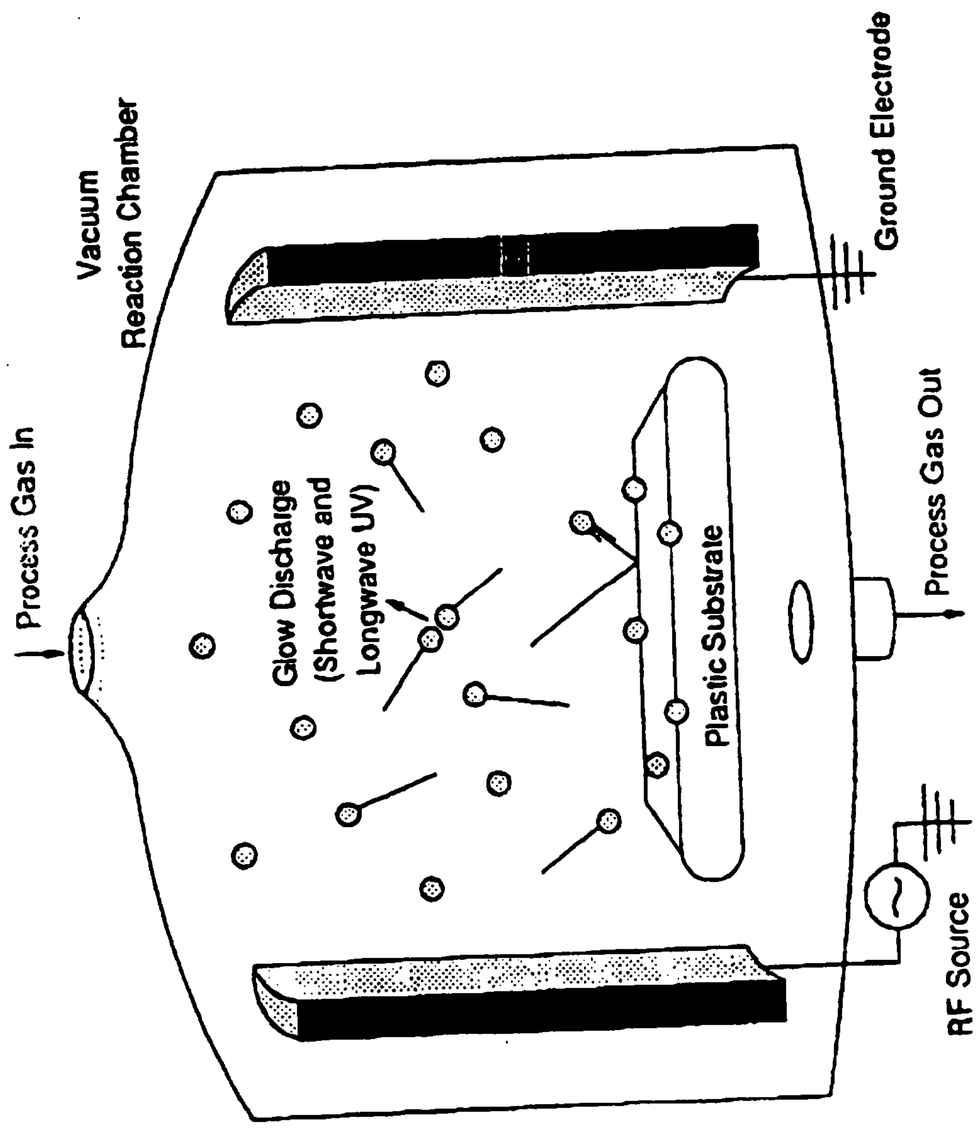
detecting a radiative signal at an intensity which meets or exceeds a predetermined intensity, wherein a radiative signal at said predetermined intensity correlates with the presence of coating of a predetermined amount of said bioactive agent covalently bound to said surface, said coating is therapeutic when said surface is exposed to blood flow continuous with bodily blood circulation.

29. A method for treating a surface of a medical device to promote thrombosis comprising steps:

functionalizing a surface of a medical device which surface is exposed to blood not in continuous flow with bodily blood circulation with a first reactive group, contacting said surface with an thrombogenic agent capable of reacting with said first reactive group, and causing said thrombogenic agent to react with said first reactive group to covalently bind said thrombogenic agent to said surface

to form a coating on said surface which is effective to promote the formation of thrombus when said surface is exposed to blood not in continuous flow with bodily blood circulation.

FIG 1



Typical Plasma Chamber

FIG 2

Plasma Surface modification System

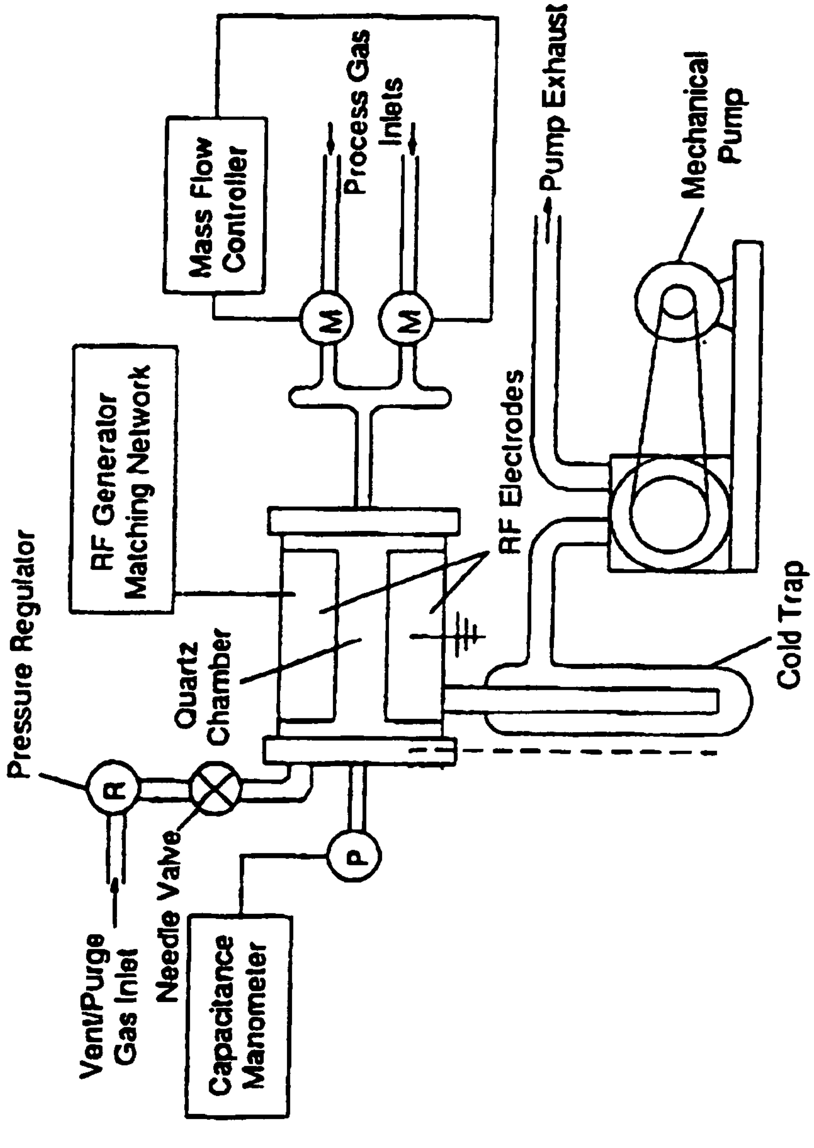


FIG 3

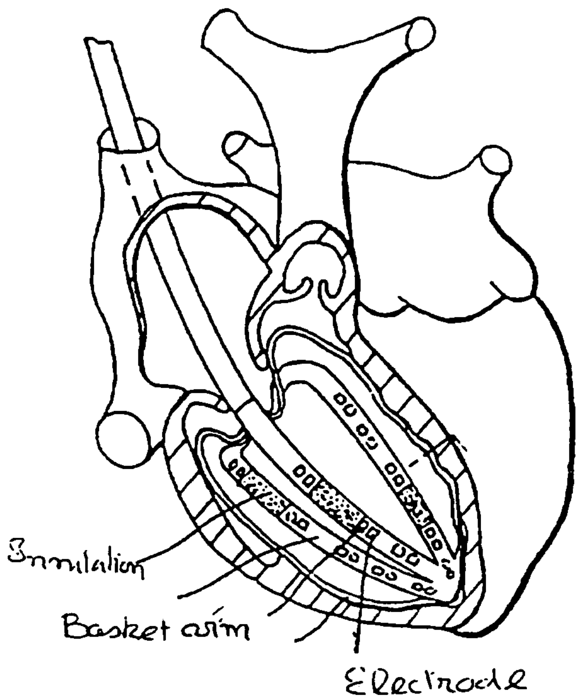
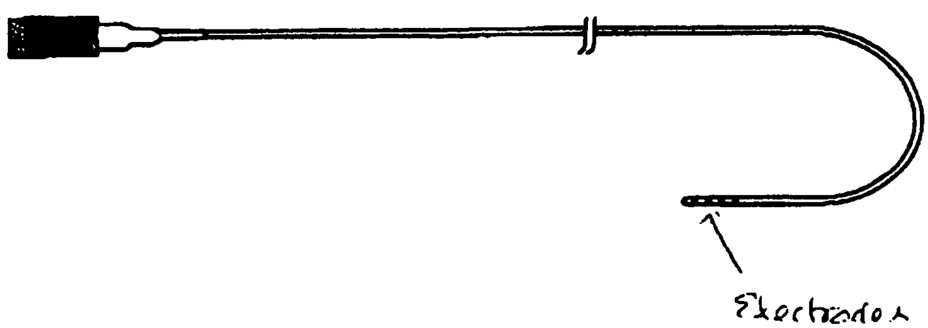
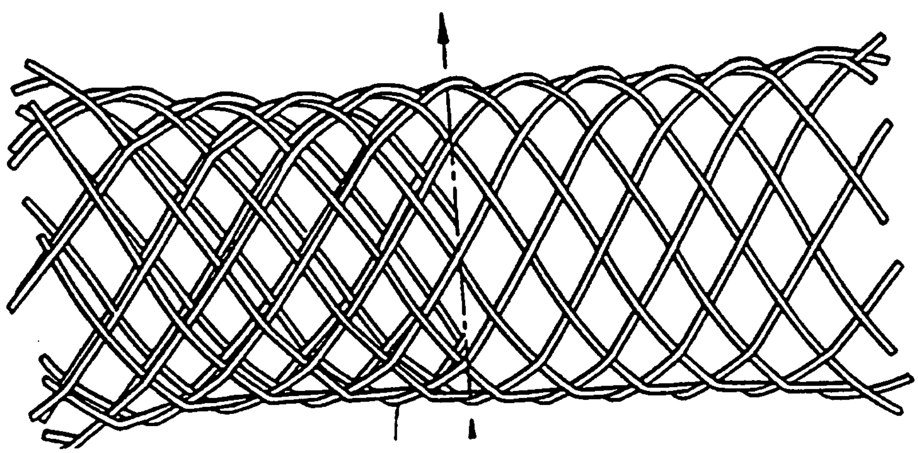


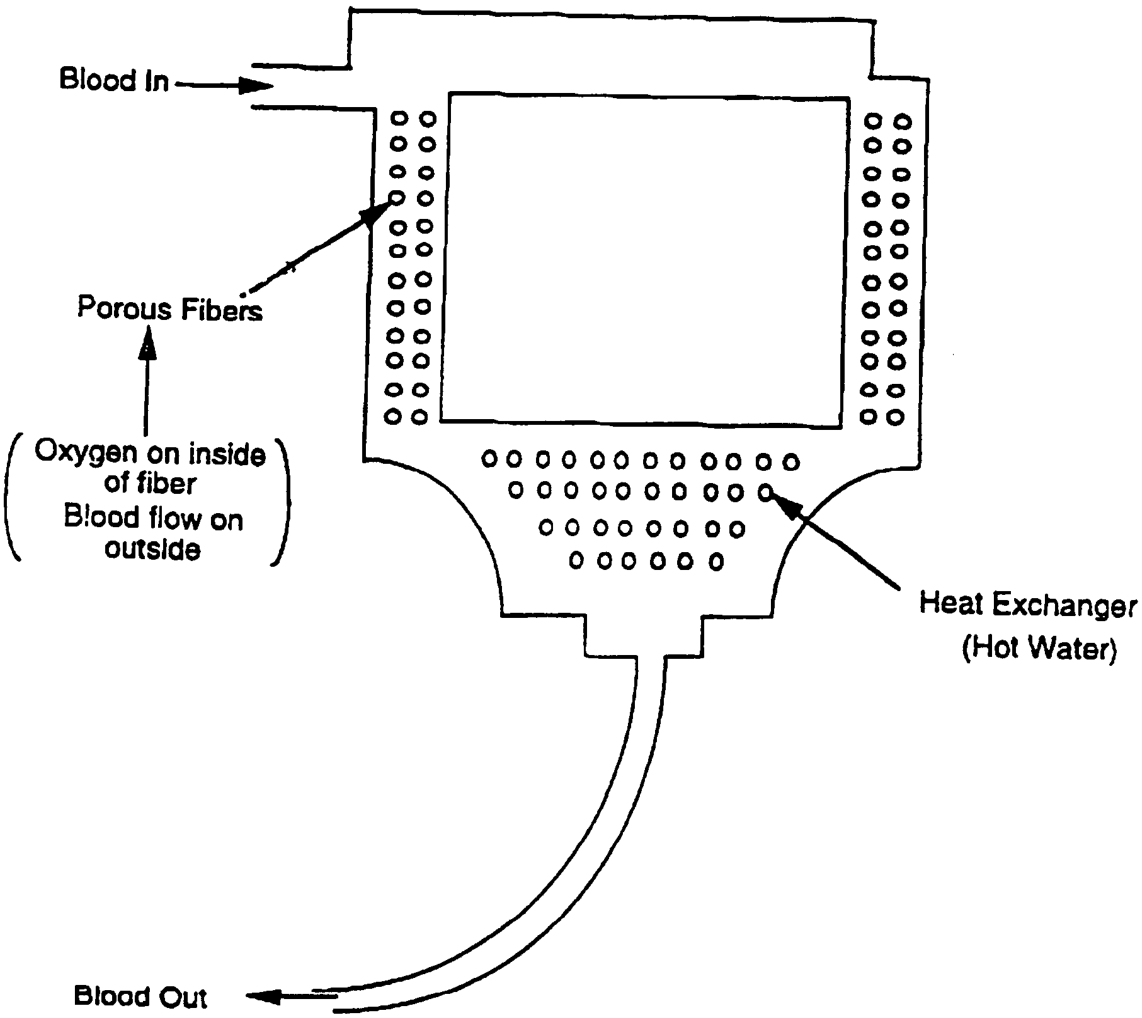
FIG 4



Typical Electrophysiology Catheter

FIG 5





BLOOD OXYGENATOR

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US95/13171

A. CLASSIFICATION OF SUBJECT MATTER

IPC(6) :A61K 9/00; C12N 11/08
US CL : 424/ 400; 623/ 1, 11; 427/ 2; 436/ 501
According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

U.S. : 424/ 400; 623/ 1, 11; 427/ 2; 436/ 501

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	US, A, 5,324,647 (RUBENS ET AL) 28 June 1994, entire document.	1-12, 15-21, 23-25, 27 and 29
Y	US, A, 5,217,492 (GUIRE ET AL) 08 June 1993, entire document.	13-14, 22, 26 and 28

☐ Further documents are listed in the continuation of Box C. ☐ See patent family annex.

* Special categories of cited documents:

"A" document defining the general state of the art which is not considered to be part of particular relevance

"E" earlier document published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
17 JANUARY 1996	08 FEB 1996

Name and mailing address of the ISA/US	Authorized officer
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